PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
RJW/CP6268841		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/005421	22.12.2004	22.12.2003

International Patent Classification (IPC) or national classification and IPC
C07C405/00, C07C59/90, A61K31/5575, A61K31/192, A61P37/00

Applicant
PHARMAGENE LABORATORIES LIMITED et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.10.2005	10.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Goetz, G Telephone No. +49 89 2399-8105

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/005421

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-84	as originally filed

Claims, Numbers

1-18	received on 21.10.2005 with letter of 20.10.2005

Drawings, Sheets

1-9	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9,10,15-18

because:

☒ the said international application, or the said claims Nos. 9,10,15-18 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-18
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-8,11-14
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

D1: SZCZEPAN JOZEFOWSKI ET AL.: "Exogenous but not endogenous prostanoids regulate cytokine secretion from murine bone marrow dendritic cells: EP2, DP, and IP but not EP1, EP3, and FP prostanoid receptors are involved" INTERNATIONAL IMMUNOPHARMACOLOGY, vol. 3, 1 June 2003 (2003-06-01), pages 865-878, XP002325093

D2: NIALS A T ET AL: "AH13205, A SELECTIVE PROSTANOID EP2-RECEPTOR AGONIST" CARDIOVASCULAR DRUG REVIEWS, NEVA PRESS, BRANFORD, CT, US, vol. 11, no. 2, 1993, pages 165-179, XP009004866 ISSN: 0897-5957

D3: VANCHERI C ET AL: "The lung as a privileged site for the beneficial actions of PGE2" TRENDS IN IMMUNOLOGY, ELSEVIER, CAMBRIDGE, GB, vol. 25, no. 1, January 2004 (2004-01), pages 40-46, XP004481206 ISSN: 1471-4906

D4: KANDA N ET AL: "Prostaglandin E2 suppresses CCL27 production through EP2 and EP3 receptors in human keratinocytes" JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, MOSBY - YEARLY BOOK, INC, US, vol. 114, no. 6, December 2004 (2004-12), pages 1403-1409, XP004666387 ISSN: 0091-6749

D5: HILLOCK C J ET AL: "INHIBITORY PROSTANOID EP RECEPTORS IN HUMAN NON-PREGNANT MYOMETRIUM" EUROPEAN JOURNAL OF PHARMACOLOGY, AMSTERDAM, NL, vol. 378, no. 1, 28 July 1999 (1999-07-28), pages 99-108, XP001124311 ISSN: 0014-2999

D6: WO 03/037433 A (ALLERGAN, INC) 8 May 2003 (2003-05-08)

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. For the assessment of the present claims 9, 10, 15 to 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however,

claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Claims 1 to 10, 14,18:

The stereoisomers of present claims 1 to 3 are not disclosed in any of the prior art documents. In particular D5 and D6 disclose the racemate AH13205 which has 3 chiral centres and exists thus in 8 stereoisomeric forms.
However, neither the isolated stereoisomers are disclosed nor is a method of separating these stereoisomeric forms disclosed in the prior art.
The subject matter of present claims 1 to 3 and 4 to 10 and 14 and 18 is thus novel over said prior art (PCT Article 33.2).

In view of D5 and D6 the underlying problem can be defined by the provision of the single stereoisomers of AH13205.
This problem can be considered to be solved as shown in examples 2, 4 and 5 and the figures.
It could be furthermore shown that the stereoisomers show an improved agonist activity and EP_2 selectivity compared with the racemate (see table 5).
Having regard to the fact that 8 stereoisomeric forms of AH13205 exist and due to the improved activity of the stereoisomers the subject matter of present claims 1 to 10 and 14 and 18 is regarded to be based on an inventive step over the prior art (PCT Article 33.3).

Industrial applicability is given for present claims 1 to 8 and 14 (PCT Article 33.4).

2. Claims 11 to 13, 15 to 18:

None of the prior art D1, D2 and D5, D6 disclose that an EP_2 agonist may inhibit the release of IL-2 or IFN-gamma or may inhibit the human T-cell activation.
Furthermore, none of these prior art documents disclose the use of an EP_2 agonist in the treatment of psoriasis.
The subject matter of present claims 11 to 13 and 15 to 17 is thus considered to relate to novel subject matter (PCT Article 33.2).

There is no indication in any of the prior art documents D1, D2, D5, D6 to be found which would render the subject matter of present claims 11 to 13, 15 to 17 obvious.
The subject matter of present claims 11 to 13, 15 to 17 is thus considered to be based on an inventive step (PCT Article 33.3).

Industrial applicability is given for present claims 11 to 14 (PCT Article 33.4).

Re Item VI
Certain documents cited

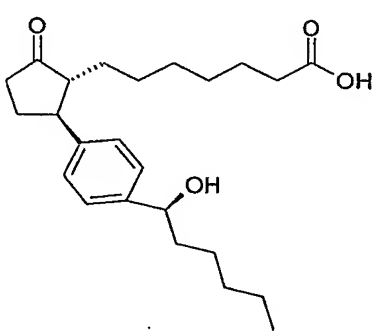
1. The documents D3 and D4 disclose that PGE_2 which represents an EP2 receptor agonists acts as an inhibitor of the release of inflammation mediators and can be used in the treatment of immunological disorders such as psoriasis (see D3: page 42 l.h.col.; see D4: last paragraph)

Re Item VIII
Certain observations on the international application

1. The characterisation of a compound as being "a chemically protected form" or "a prodrug thereof" is considered not to be clear in the sense of Article 6 PCT: a chemical compound has to be unambiguously defined by structural features.

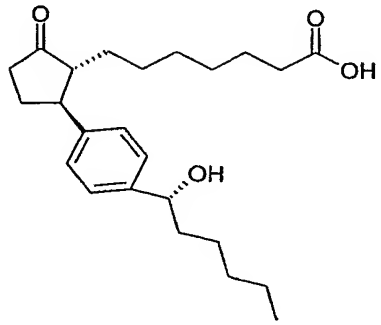
CLAIMS

1. A compound selected from one of the following:



(1R,2S)-2-[4-(1-(S)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSS]

; or

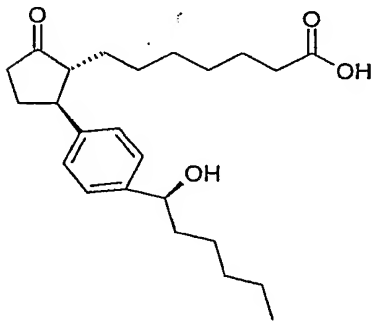


(1R,2S)-2-[4-(1-(R)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSR]

,

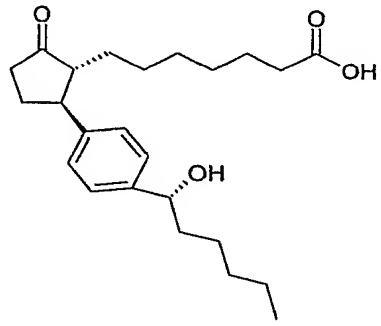
or a salt, solvate, chemically protected form or prodrug thereof.

2. (*trans*-2-[4-(1-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid, of which at least 90% by weight is selected from one of the following forms:



(1R,2S)-2-[4-(1-(S)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSS]

; or



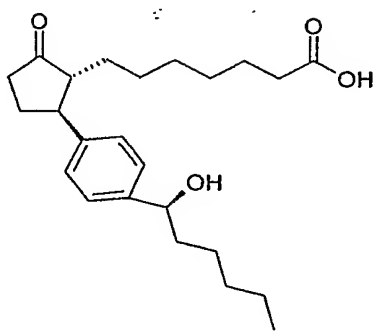
(1R,2S)-2-[4-(1-(R)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSR]

,

or a salt, solvate, chemically protected form or prodrug thereof.

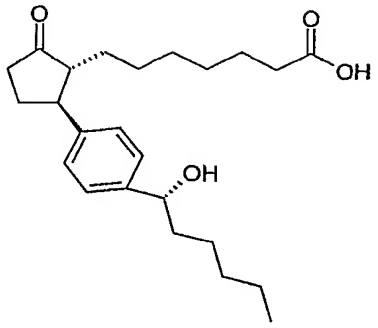
3. 2-[4-(1-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid, of which at least 80% by weight

is in one of the following forms:



(1R,2S)-2-[4-(1-(S)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSS]

; or



(1R,2S)-2-[4-(1-(R)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSR]

,

or a salt, solvate, chemically protected form or prodrug thereof.

4. A method of making a compound according to any one of claims 1 to 3.

5. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, for use in a method of therapy.

6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.

7. The use of a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by agonism of an EP_2 receptor.

8. The use according to claim 7, wherein the condition alleviated by agonism of an EP_2 receptor is selected from the group consisting of: glaucoma, dysmenorrhoea and pre-term labour.

9. A method of treating a condition which can be alleviated by agonism of an EP_2 receptor, which method comprises administering to a patient in need of treatment an effective amount of a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof.

10. The method according to claim 9, wherein the condition alleviated by agonism of an EP_2 receptor is selected from the group consisting of: glaucoma, dysmenorrhoea and pre-term labour.

11. The use of an EP_2 receptor agonist, or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by the inhibition of:

(i) human T-cell activation (proliferation);

(ii) the release of IL-2; or

(iii) the release of IFNγ.

12. The use according to claim 11, wherein the condition is a condition alleviated by the inhibition of:

(ii) the release of IL-2; or.

(iii) the release of IFNγ.

13. The use of an EP_2 receptor agonist, or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of psoriasis.

14. A use according to any one of claims 11 to 13, wherein the EP_2 receptor agonist is a compound of any one of claims 1 to 3.

15. A method of treating a condition which can be alleviated by the inhibtion of:

(i) human T-cell activation (proliferation);

(ii) the release of IL-2; or

(iii) the release of IFNγ;

which method comprises administering to a patient in need of treatment an effective amount of an EP_2 receptor agonist, or a pharmaceutically acceptable salt thereof.

16. The method according to claim 15, wherein the condition is a condition which can be alleviated by the inhibition of:

(ii) the release of IL-2; or

(iii) the release of IFNγ.

17. A method of treating a psoriasis, which method comprises administering to a patient in need of treatment an effective amount of an EP_2 receptor agonist, or a pharmaceutically acceptable salt thereof.

18. A method according to any one of claims 15 to 17, wherein the EP_2 receptor agonist is a compound of any one of claims 1 to 3.